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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/722,587 | 11/28/2003 | Robert D. Rosenberg | P-6170-US | 5678 |

49443 7590 09/15/2009

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| EXAMINER | |
|---|---|
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| ART UNIT | PAPER NUMBER |
| 1623 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 09/15/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/722,587 | ROSENBERG ET AL. | |
| | Examiner | Art Unit | |
| | SCARLETT GOON | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *3-5,7,9,19,21,32-38,40-42,44,49-62,64 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,8,10-18,20,22-31,39,43,45-48 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4 June 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

This Office Action is in response to Applicants' Amendment and Remarks filed on 4 June 2009 in which claims 1, 2, 6-17, 39, 42-44 and 46-48 are amended to change the scope and breadth of the claims.

Claims 1-65 are pending in the instant application.

Claims 3-5, 19, 21, 32-38, 40, 41, 49-62, 64 and 65 were previously withdrawn from further consideration in the Office Action dated 8 December 2008 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or nonelected species, there being no allowable generic or linking claim.

Applicants' amendment to claims 7, 9, 42 and 44 to further clarify what Applicants intend to claim (in response to 35 USC § 112 rejections), a method of preparing a sulfated polysaccharide with at least one enzyme and at least one chemical, or a method of synthesizing polysaccharide (11), renders the claims to be drawn to a non-elected species. Thus, claims 7, 9, 42 and 44 are also withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1, 2, 6, 8, 10-18, 20, 22-31, 39, 43, 45-48 and 63 are examined on its merits herein.

***Priority***

This application claims priority to U.S. provisional application no. 60/429946 filed on 27 November 2002 and U.S. provisional application no. 60/456889 filed on 21 March 2003.

***Information Disclosure Statement***

The information disclosure statement (IDS) dated 4 June 2009 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

***Objections Withdrawn***

Applicants' amendment, filed 4 June 2009, with respect to the objection of claims 18, 20 and 22-31 as being of improper dependent form because a multiple dependent claim is dependent from another multiple dependent claim, has been fully considered and is persuasive because the multiple dependencies have been removed.

These objections have been **withdrawn**.

***Rejections Withdrawn***

Applicants' arguments, filed 4 June 2009, with respect to the rejection of claims 1-31 under 35 USC § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention because the recitation "incompletely sulfated polysaccharide" in claims 1 and 2 is unclear, has been

fully considered and is persuasive. One of ordinary skill in the art readily understands that this refers to an O- or N-site that is not yet sulfated on the polysaccharide. These rejections have been **withdrawn**.

Applicants' arguments and amendments, filed 4 June 2009, with respect to the rejection of claims 7, 9 and 44 under 35 USC § 112, second paragraph, as being indefinite for insufficient antecedent basis for the limitations "chemical reagents" or "nitrous acid and sodium borohydride," has been fully considered and is persuasive because the claims use the transitional phrase "comprising" which permits additional elements. As indicated above, in view of Applicants' arguments and clarification to the claims, these claims are withdrawn from further consideration for being drawn to a non-elected species (elected species was a method encompassing only enzymes). These rejections have been **withdrawn**.

Applicants' amendment, filed 4 June 2009, with respect to the rejection of claim 39 under 35 USC § 112, second paragraph, as being incomplete for omitting essential steps and for being indefinite as it is unclear what is being synthesized, has been fully considered and is persuasive because the claim has been amended to recite a method of synthesizing polysaccharide (15) involving the steps outlined in the amended claim. These rejections have been **withdrawn**.

Applicants' amendment, filed 4 June 2009, with respect to the rejection of claim 39 under 35 USC § 112, second paragraph, as being incomplete for omitting essential steps and for being indefinite as it is unclear what is being synthesized, has been fully considered and is persuasive because the claim has been amended to recite a method

of synthesizing polysaccharide (15) involving the steps outlined in the amended claim. These rejections have been **withdrawn**.

Applicants' amendment, filed 4 June 2009, with respect to the rejection of claim 42 under 35 USC § 112, first paragraph, for failing to comply with the written description requirement, has been fully considered and is persuasive because the claim has been amended to recite a method of 2-*O*-sulfating polysaccharide (11) comprising the steps of treatment of polysaccharide (10) with an epimerase and 2-OST1. As indicated above, in view of Applicants' arguments and clarification to the claims, this claim is withdrawn from further consideration for being drawn to a non-elected species (elected species was Pentasaccharide (15). These rejections have been **withdrawn**.

Applicant's amendment, filed 4 June 2009, with respect to the rejection of claims 11-13, 18, 20 and 22-31 under 35 USC § 101, for being directed to non-statutory matter, has been fully considered and is persuasive because the claim has been amended to recite an "*in vitro* method." These rejections have been **withdrawn**.

The following are new ground(s) or modified rejections necessitated by Applicants' amendment, filed on 4 June 2009, wherein the limitations in pending claims 1, 39 and 63 as amended now have been changed; claims 2, 6, 8, 10-18, 20, 22-31, 43 and 45-48 depend from claim 1. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, dated 8 December 2008, have been modified and are listed below.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 8, 10 and 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by journal publication by Pikas (IDS dated 26 December 2006).

Pikas teaches enzymes involved in the biosynthesis and degradation of heparin-related polysaccharides, namely heparanase, which degrades heparin and heparan sulfate, and N-deacetylase/N-sulfotransferase (NDST), which generates the complex structure of heparin and heparan sulfate. In determining the substrate recognition properties of heparanase, Pikas modified a polysaccharide obtained from the K5 strain of *Escherichia coli* having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$ (p. 306, column 1, C-2). This K5 polysaccharide is identical to the unmodified parts of heparin sulfate. The K5 polysaccharide was modified in a controlled stepwise fashion by combining different treatments; (1) chemical *N*-deacetylation and *N*-sulfation, (2) enzymatic GlcA C5-epimerization and (3) chemical O-sulfation.

Thus, the modification of a polysaccharide having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$, obtained from the K5 strain of *Escherichia coli*, by chemical *N*-deacetylation and *N*-sulfation, enzymatic GlcA C5-epimerization, and chemical O-sulfation, disclosed by Pikas, anticipates claims 1, 2, 8, 10 and 13-17.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Section [0001]**

Claims 6, 11, 12, 18, 20, 22-31, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Pikas (IDS dated 26 December 2006) as applied to claims 1, 2, 8, 10 and 13-17, further in view of journal publication by Esko *et al.* (PTO-892, Ref. U).

The teachings of Pikas were as disclosed above in the claim rejections under 35 USC § 102.

The teachings of Pikas differ from that of the instantly claimed invention in that O-sulfation of the polysaccharide was accomplished chemically rather than enzymatically.

Esko *et al.* teach that the biosynthesis of heparan sulfate depends on many enzymes, including multiple glycotransferases, sulfotransferases, and an epimerase (p. 170, column 2, last paragraph). Most of the enzymes that participate in heparan sulfate biosynthesis have been purified and molecularly cloned, including four *N*-deacetylase/*N*-sulfotransferases, five 3-*O*-sulfotransferases and three 6-*O*-sulfotransferses (p. 171, column 1, last paragraph). While the enzymes of the same subfamily catalyze the same reaction, they differ in their substrate specificity. Additionally, one 2-*O*-sulfotransferase and one epimerase are known (p. 171, column 2, first full paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Pikas, concerning the modification of a polysaccharide having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$ by chemical *N*-deacetylation and *N*-sulfation, enzymatic GlcA C5-epimerization, and chemical *O*-sulfation, with the teachings of Esko *et al.*, regarding the availability of many enzymes

involved in the biosynthesis of heparan sulfate. Since Esko *et al.* teach that many of the enzymes that participate in heparan sulfate biosynthesis have been purified and molecularly cloned, and that their substrate specificities have been characterized, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the chemical modification steps for modification of the polysaccharide disclosed in Pikas (chemical *N*-deacetylation and *N*-sulfation and chemical *O*-sulfation), with enzymatic steps using the enzymes disclosed by Esko *et al.* Since it is well-known to one of ordinary skill in the art that the use of enzymes results in a defined product as enzymes are generally substrate specific, and also avoids the use of organic reagents which are typically hazardous to the health, one would have been motivated to combine the teachings and substitute enzymatic modification in place of chemical modification. Furthermore, as chemical *O*-sulfation can be non-specific, the use of enzymes allows one to sulfate only specific sites on the polysaccharide depending on the substrate specificity of the sulfotransferase, allowing one to have better control over the generated product.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

**Section [0002]**

Claims 39, 43, 45, 48 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Pikas (IDS dated 26 December 2006) as applied to claims 1, 2, 8, 10 and 13-17, further in view of journal publication by Kusche

*et al.* (of record), in view of journal publication by Habuchi *et al.* (PTO-892, Ref. V), in view of journal publication by Nader *et al.* (of record), in view of journal publication by Myette *et al.* (of record).

The teachings of Pikas were as disclosed above in the claim rejections under 35 USC § 102.

While Pikas teaches the use of a polysaccharide having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$, from the K5 strain of *Escherichia coli*, which has a structure identical to unmodified heparin sulfate, for the synthesis of polysaccharides, Pikas does not teach the synthesis of pentasaccharide (15) from the *E. coli* polysaccharide using the instantly claimed method.

Kusche *et al.* teach the various substituents of heparin that are important for antithrombin binding. The polysaccharide chains of heparin and heparan sulfate display extensive structural variability, with potential for specific interaction with other macromolecules via the presence of unique sequences (p. 7400, column 2, paragraph 1). One such interaction is the antithrombin-binding region, essential for the blood anticoagulant activity of heparin. The structure of the antithrombin-binding region is shown in Figure 1 (p. 7401, column 1). The structure of the pentasacharide sequence is largely nonvariable and cannot be modified without dramatic loss of biological activity (p. 7400, column 2, paragraph 1). As indicated, the 3-*O*-sulfate group of unit III is essential for the high affinity binding of heparin to antithrombin and is a marker component of the antithrombin-binding region (Fig. 1 legend). The 6-*O*-sulfate group of unit I and the N-sulfate groups of units III and V are also critically important for

antithrombin binding. The modification of the amino group of unit I with either an acetate or sulfate group does not affect antithrombin binding. Additionally, the sulfate groups at C-2 and C-6 of units IV and V, respectively, are less essential for antithrombin binding. The structure of Figure 1 wherein R" of unit 1 is an acetate group, R' of unit III is a sulfate group, and the sulfate group at C-6 of unit V is a hydroxyl group, is the same as pentasaccharide (15) of instant claim 39.

Habuchi *et al.* teach that various enzymes participating in the biosynthesis of heparan sulfate have been purified to homogeneity and cloned (p. 65, paragraph 2). Studies of the heparan sulfate enzymes offered new information regarding the specificity of the enzymes, and further confirmed the biosynthetic process as depicted in Figure 1. (p. 69). As indicated, the biosynthesis of heparan sulfate depends on multiple glycotransferases, sulfotransferases, and an epimerase. Most of these enzymes that participate in heparan sulfate biosynthesis have been purified and molecularly cloned, including *N*-deacetylase/*N*-sulfotransferases, 3-*O*-sulfotransferases, 6-*O*-sulfotransferses, a 2-*O*-sulfotransferase, and an epimerase (entire article). *N*-deacetylase/*N*-sulfotransferase is a bifunctional enzyme responsible for N-deacylating the GlcNAc unit followed by *N*-sulfation of the resulting amino group (p. 70-72, section E-2-1). Enzymes of this subfamily differ in the extent of *N*-sulfation. The 3-*O*-sulfotransferases, 6-*O*-sulfotransferases and 2-*O*-sulfotransferase catalyze the transfer of a sulfate group from PAPS to the corresponding position on the heparin chain. Although the 2-*O*-sulfotransferase generally only catalyzes the transfer of a sulfate group to C-2 of an iduronic acid residue, C-2 sulfation of GlcA may occur during a

transient period after *N*-deacetylation/*N*-sulfation of GlcNAc and before epimerization of GlcA (p. 74, first full paragraph). Glucuronyl C5-epimerase catalyzes the conversion of D-glucuronic acid to L-iduronic acid units (p. 69-70, section E-1). The glucuronyl C5-epimerase requires preceding *N*-sulfation of the neighboring *N*-acetylglucosamine.

Nader *et al.* teach the purification and substrate specificity of heparitinase I and heparitinase II from *Flavobacterium heparinum*. These enzymes are responsible for the degradation of glycosaminoglycans. Heparitinase I acts on *N*-acetylated or *N*-sulfated glucosaminido-glucuronic acid linkages of heparan sulfate (abstract). Heparitinase II acts preferentially upon *N*-6-sulfated and/or *N*-acetylated, 6-sulfated glucosaminido-α-1,4-glucuronic acid linkages (p. 16813, column 1, last paragraph).

Myette *et al.* teach the cloning and substrate specificity of the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase from *Flavobacterium heparinum*. This enzyme hydrolyzes the unsaturated $\Delta^{4,5}$ uronic acid at the nonreducing end of oligosaccharides that result from prior heparinase (and heparitinase) eliminative cleavage (abstract). It discriminates both on the basis of glycosidic linkage and sulfation pattern (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Pikas, concerning the modification of a polysaccharide having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$ by chemical *N*-deacetylation and *N*-sulfation, enzymatic GlcA C5-epimerization, and chemical *O*-sulfation, with the teachings of Kusche *et al.*, regarding the importance of certain substituents of heparin for antithrombin binding, with the teachings of Habuchi *et al.*, regarding the specificity of *N*-deacetylase/*N*-sulfotransferase, *O*-sulfotransferases, and

glucuronyl C5-epimerase, with the teachings of Nader *et al.*, regarding the specificity of heparitinase I and heparitinase II, with the teachings of Myette *et al.*, regarding the cloning and substrate specificity of the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase. Since Kushe *et al.* teach that heparin, which is used as an anticoagulant, is extensively variable and that only a pentasaccharide structure is critical for antithrombin-binding, one of ordinary skill in the art would have been motivated to synthesize the pentasaccharide structure for use as a possible anticoagulant drug in an effort to overcome the variabilities observed with heparin. Since Pikas teach the chemoenzymatic synthesis of various sulfated polysaccharides by modification of a polysaccharide isolated from *E. coli*, one would have been motivated to use this *E. coli* polysaccharide as the starting point for synthesis of the antithrombin-binding region since Pikas teaches that the *E. coli* polysaccharide is identical to the unmodified parts of heparin sulfate. Additionally, one would have been motivated to use the *E. coli* polysaccharide as a starting material rather than synthesize the pentasaccharide from monosaccharide units as it is well-known in the art that the chemical synthesis of a pentsaccharide is quite laborious and cumbersome due to the multiple stereocenters involved. Although one would argue that the use of enzymes would overcome the stereoselectivity issues of chemical synthesis, enzymes for the synthesis of the pentasaccharide unit, or even heparin, from a monosaccharide unit, is not known. Thus, as the biosynthesis of heparin sulfate is well-known, and the enzymes involved in the biosynthesis of heparin sulfate has been purified, cloned, and characterized, one of ordinary skill in the art would have been motivated to model their synthesis of the

pentasaccharide after a known pathway, beginning with a polysaccharide that is the same as the native starting polysaccharide, $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$. With regards to the order of the reaction steps in the instantly claimed method, as the enzymes involved in heparin sulfate have been characterized, one of ordinary skill in the art would necessarily to take into account the substrate specificity of each enzyme to determine the proper sequence of enzymatic reactions that must be done in order to arrive at the desired pentasaccharide structure.

Since the *E. coli* polysaccharide must be degraded from its extensive chain down to the pentasaccharide unit, one would have been motivated to look at the use of heparin degrading enzymes which have specificity for certain structural units, thereby resulting in a degraded saccharide with a defined structure. Known heparin degrading enzymes, such as heparinase and heparitinase, result in shorter saccharide structures bearing a terminal unsaturated uronic acid residue. Thus, one would have been motivated to use $\Delta^{4,5}$ unsaturated glycuronidase in order to remove the terminal unsaturated uronic acid residue so as to obtain the desired pentassacharide. With regards to which step in the enzymatic synthesis of the pentasaccharide one would incorporate the use of heparitinase and glycuronidase, one of ordinary skill in the art would be capable of determining this based on an understanding of the substrate specificity of all the enzymes involved.

With regards to the specific subfamily of each enzyme used in each step of the instantly claimed method, as the various enzymes involved in heparin sulfate biosynthesis have been cloned and characterized, and it is known that each enzyme of

a subfamily differ in their substrate specificity or degree of enzymatic activity, absent a showing of criticality, it is considered *prima facie* obvious for one of ordinary skill in the art to identify the specific enzyme, from among the different enzymes of the subfamily, for use in the enzymatic synthesis of the pentasaccharide.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

The following rejections of record in the previous Office Action are maintained.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of brackets and/or bonds that are not attached to any atoms to denote Polysaccharide 1, Polysaccharide 10 and Polysaccharide 11 renders claim 39 herein indefinite. It is unclear whether the bonds that are not attached to any atoms indicate that the structure is repeated or whether an atom was not drawn. Furthermore, the presence of brackets generally represent repeating units. However, this is unclear as the number of repeating units is not denoted next to the brackets, as is typically the case.

*Response to Arguments*

Applicant's arguments, filed 4 June 2009, with respect to the rejection of claim 39 made under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, have been fully considered but they are not persuasive.

Applicants argue that one of ordinary skill in the art would recognize that the use of bonds not attached to any atoms to denote that the polysaccharides disclosed is for recognition that the unit at this point in the synthesis is part of a larger polysaccharide chain. This argument is not persuasive because in the absence of any indication as to what the bond is attached to, one of ordinary skill in the art would view that portion of the structure to represent a skeletal formula, thereby suggesting that a methyl group is attached to the end of the bond (PTO-892, Ref. W). Thus, contrary to Applicants' arguments, one of ordinary skill in the art would not readily recognize that the indicated polysaccharide is part of a larger polysaccharide structure.

The rejection is still deemed proper and therefore adhered to.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 6-10 and 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by journal publication by Wei *et al.* (of record).

Wei *et al.* disclose that the biosynthesis of heparin sulfate utilizes a single protein that possesses both *N*-deacetylase and *N*-sulfotransferase activities (abstract). Towards characterizing the activity of the *N*-deacetylase, the release of [$^3$H]acetate from *N*-[$^3$H]acetylated polysaccharide derived from *Escherichia coli* K5 was measured (p. 3886, column 1, first paragraph).

It is noted that Wei *et al.* do not disclose the amount of sulfates present in the *Escherichia coli* K5 polysaccharide. However, as evidenced by Vann *et al.* (of record), the capsular polysaccharide from *Escherichia coli* 010:K5:H4 is a repeating disaccharide unit comprising 4-β-glucuronyl-1,4-α-N-acetylglucosaminyl residues (abstract) that is similar to that of desulfo-heparin (p. 363, column 1, paragraphs 2 and 3). Wei *et al.* indicates that heparan sulfate and heparin only differ in sulfate content and iduronic acid content (p. 3888, column 1, first full paragraph).

Thus, the assay used in characterizing *N*-deacetylase activity, wherein an acetate residue is removed from the *N*-acetylated polysaccharide of *Escherichia coli* K5, anticipates the method of preparing a sulfated polysaccharide in claims 1, 2, 6-10 and 13-17.

*Response to Arguments*

Applicant's arguments, filed 4 June 2009, with respect to the rejection of claims 1, 2, 6-10 and 13-17 made under 35 USC § 103(a) as being unpatentable over Wei *et al.*, have been fully considered but they are not persuasive.

Applicants argue that the Wei *et al.* reference only teaches one step in the sulfation of a polysaccharide, and does not teach that the sulfated polysaccharide is "capable of binding to a binding partner." Applicants argue that the incompletely sulfated polysaccharide is unable to bind to proteins known in the art. These arguments are not persuasive because the product obtained from *N*-deacetylation/*N*-sulfation can be recognized by a GlcA C5-epimerase. As disclosed by Habuchi *et al.*, the glucuronyl C5-epimerase requires preceding N-sulfation of the neighboring *N*-acetylglucosamine for catalysis of GlcA to IdoA (p. 69-70, section E-1). Applicants' argument appears to limit sulfated polysaccharide binding to only those proteins that recognize heparan sulfate. However, as indicated in the Specification as originally filed, "the term "binding partner" refers to any molecule that binds to a polysaccharide anc can include a protein, peptide, polysaccharide, antibody, etc." Thus, the GlcA C5-epimerase is deemed to meet the claim limitations of a "binding partner."

The rejection is still deemed proper and therefore adhered to.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either

anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 6, 8, 10-13, 18, 20, 22-24 and 26-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13, 18, 19, 24, 29 and 30 of copending application no. 11/204391.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for the preparation of *N*-sulfate derivatives of non-sulfated *N*-acetyl heparosan polysaccharides comprising the steps of (a) contacting a non-sulfated *N*-acetyl heparosan polysaccharide witn *N*-deacetylase-*N*-sulfotransferase and glucuronosyl C-5 epimerase to generate an iduronic acid-enriched polysaccharide; (b) contacting the product in (a) with 6-*O*-sulfotransferase and 3-*O*-sulfotransferase; and (c) isolating the product of (b) which yields N-deacetylated N-sulfate derivatives of non-sulfated N-acetyl heparosan (claims 13 and 24). The 3-*O*-sulfotransferase is 3-OST1, 3-OST2, 3-OST3, 3-OST4 or 3-OST5 (claims 18 and 29). The 6-*O*-sulfotransferase is 6-OST1, 6-OST2 or 6-OST3 (claims 19 and 30).

The claims of the instant application are drawn to a method of preparing a sulfated polysaccharide or heparan sulfate comprising treating an unsulfated or

incompletely sulfated polysaccharide or unsulfated heparan synthon with at least one enzyme (claims 1, 2, 8 and 10). The enzyme is selected from the group consisting of an *N*-deacetylase, an *N*-sulfotransferase, an epimerase and an *O*-sulfotransferase (claim 6). The method comprises (a) treating an unsulfated polysaccharide with an N-deacetylating reagent; (b) treating the step (a) product with an *N*-sulfating reagent; (c) treating the step (b) product with an epimerizing reagent; and (d) treating the step (c) product with at least one *O*-sulfating reagent (claims 11 and 12). The heparan synthon is a non-sulfated *N*-acetyl heparosan (claim 13). The deacetylating reagent is selected from the group consisting of a deacetylase and *N*-deacetylase-*N*-sulfotransferase (claims 18 and 20). The epimerizing reagent is selected from the group consisting of C5-epimerase (claim 22). The *O*-sulfating reagent incorporates a 3-*O*-sulfate group or a 6-*O*-sulfate group (claims 23, 24 and 26). The *O*-sulfating reagent is a 3-*O*-sulfotransferase selected from the group consisting of 3-OST1, 3-OST2, 3-OST3, 3-OST4, 3-OST5 and 3-OST6 (claims 27 and 28). The *O*-sulfating reagent is a 6-O-sulfotransferase selected from the group consisting of 6-OST1, 6-OST2 and 6-OST3 (claims 29 and 30).

Thus, the instant claims 1, 2, 6, 8, 10-13, 18, 20, 22-24 and 26-30 are seen to be anticipated by claims 13, 18, 19, 24, 29 and 30 of copending application no. 11/204391.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 6, 8, 10-18, 20 and 22-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6, 16, 17, 19, 20, 23, 29, 39, 41, 42, 81, 85 and 88 of copending application no. 10/986058.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for the synthesis of an epimerically enriched form of a sulfated heparosan polysaccharide, comprising an acceptor heparosan polysaccharide with PAPS, at least one sulfotransferase, a p-nitrophenyl sulfate donor, an arylsulfatase and an epimerase (claims 1, 23 and 81). The epimerase is a glucuronosyl C5 epimerase (claims 6 and 29). The sulfated heparosan is isolated (claims 16). The sulfotransferase is an *N*-deacetylase-*N*-sulfotransferase, heparin sulfate 2-*O*-sulfotransferase, 6-*O*-sulfotransferase, 3-*O*-sulfotransferase, 2-*O*-sulfotransferase, or a combination thereof (claims 17 and 39). The 3-*O*-sulfotransferse is 3-OST1 (claims 19, 41 and 88). The 6-*O*-sulfotransferase is 6-OST1, 6-OST2 or 6-OST3 (claims 20, 42 and 85).

The claims of the instant application are drawn to a method of preparing a sulfated polysaccharide or heparan sulfate comprising treating an unsulfated or incompletely sulfated polysaccharide or unsulfated heparan synthon with at least one enzyme (claims 1, 2, 8 and 10). The enzyme is selected from the group consisting of an *N*-deacetylase, an *N*-sulfotransferase, an epimerase and an *O*-sulfotransferase (claim 6). The method comprises (a) treating an unsulfated polysaccharide with an *N*-deacetylating reagent; (b) treating the step (a) product with an *N*-sulfating reagent; (c)

treating the step (b) product with an epimerizing reagent; and (d) treating the step (c) product with at least one *O*-sulfating reagent (claims 11 and 12). The heparan synthon is a non-sulfated *N*-acetyl heparosan (claim 13). The unsulfated polysaccharide or heparan synthon is isolated from a cell or *E. coli* bacteria (claims 14-17). The deacetylating reagent is selected from the group consisting of a deacetylase and *N*-deacetylase-*N*-sulfotransferase (claims 18 and 20). The epimerizing reagent is selected from the group consisting of C5-epimerase (claim 22). The *O*-sulfating reagent incorporates a 2-*O*-sulfate group, 3-*O*-sulfate group or a 6-*O*-sulfate group (claims 23-26). The *O*-sulfating reagent is a 3-*O*-sulfotransferase selected from the group consisting of 3-OST1, 3-OST2, 3-OST3, 3-OST4, 3-OST5 and 3-OST6 (claims 27 and 28). The *O*-sulfating reagent is a 6-*O*-sulfotransferase selected from the group consisting of 6-OST1, 6-OST2 and 6-OST3 (claims 29 and 30). The *O*-sulfating reagent is a 2-*O*-sulfotransferase (claim 31).

Thus, the instant claims 1, 2, 6, 8, 10-18, 20 and 22-31 are seen to be anticipated by claims 1, 6, 16, 17, 19, 20, 23, 29, 39, 41, 42, 81, 85 and 88 of copending application no. 10/986058.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

*Response to Arguments*

Although Applicants note that they disagree with the obviousness-type double-patenting rejections, they request that the provisional rejections be held in abeyance

until allowable subject matter has been identified, at which time they will consider filing a Terminal Disclaimer. Applicants request is acknowledged.

The rejections are still deemed proper and therefore maintained.

***Conclusion***

In view of the rejections to the pending claims set forth above, no claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-

270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

SCARLETT GOON
Examiner
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